

Menstruation and reproduction in women with polychlorinated biphenyl (PCB) poisoning: long-term follow-up interviews of the women from the Taiwan Yucheng cohort

Mei-Lin Yu,^a Yueliang Leon Guo,^b Chen-Chin Hsu^c and Walter J Rogan^d

Background	In 1979 in Taiwan, about 2000 people were poisoned by cooking oil contaminated with heat-degraded polychlorinated biphenyls (PCBs). Victims developed chloracne and other symptoms; the illness is called Yucheng (oil disease). The chemicals persist in the victims' bodies and some are toxic to the female reproductive system in experimental animals.
Methods	In 1993–1994, we identified the living Yucheng women and neighbourhood controls and interviewed them about their reproductive experience. Of the 596 living Yucheng women aged 30–59 years, we found 368, and interviewed 356. We identified 329 controls, and interviewed 312.
Results	Of the Yucheng women, 16% reported abnormal menstrual bleeding compared to 8% ($P < 0.05$) of control women; 4.2% versus 1.7% reported a stillbirth since 1979 ($P = 0.068$). Other characteristics of the menses, fertility, frequency of intercourse, and age at menopause appeared unaffected. More of the Yucheng women reported that one of their offspring had died during childhood (10.2% versus 6.1%, $P < 0.05$), and that they had decided to limit childbearing because of health problems (7% versus 2%, $P = 0.01$).
Conclusions	These findings suggest that high level PCB/polychlorinated dibenzofuran (PCDF) exposure has some effect on female endocrine and reproductive function.
Keywords	Polychlorinated dibenzofurans, polychlorobiphenyl compounds, rice oil, infant mortality
Accepted	24 January 2000

Polychlorinated biphenyls (PCBs) are a family of industrial compounds that were widely used as dielectric fluids in electrical transformers and capacitors, as heat exchangers or hydraulic fluids, and in a variety of other commercial applications between the 1930s and 1970s¹ when they were banned in much of the world. Mass poisonings in Japan in 1968² and in Taiwan in 1979,³ each involving about 2000 people, demonstrated that severe health consequences could arise from ingesting the compounds. In both events, PCBs used as heat exchangers

contaminated rice bran cooking oil during processing. These PCBs had been thermally degraded and were thus contaminated by polychlorinated dibenzofurans (PCDFs) and polychlorinated terphenyls and quaterphenyls.⁴ Victims in both incidents developed lesions of the skin and mucous membranes, then developed peripheral neuropathy and other signs and symptoms. The clinical syndrome following a history of having consumed the contaminated oil was called Yusho or Yucheng, 'oil disease' in Japanese and Chinese, respectively.^{2,3} In Taiwan, the victims used the contaminated cooking oil for as long as 9 months; they were estimated to have consumed about one gram of PCBs and 3.8 mg of PCDFs during that period.⁵ These chemicals are fat soluble and excreted quite slowly, and, 13 years later, an investigation of levels of the compounds among 56 Yucheng women who had borne a child showed that they still had mean levels of total PCBs 7.3 times those found in Taiwanese people with only background exposure (2820 parts per billion in fat of serum versus 386 ppb). They also had 39 times the background exposure levels for the 2,3,4,7,8 penta

^a Department of Public Health, National Cheng Kung University Medical College, Tainan, Taiwan.

^b Department of Environmental and Occupational Health, National Cheng Kung University Medical College, Tainan, Taiwan.

^c Department of Psychiatry, Tainan City Hospital, Tainan, Taiwan.

^d Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA.

Reprint requests to: Dr Yueliang Leon Guo, Department of Environmental and Occupational Health, National Cheng Kung University Medical College, 138 Sheng-Li Road, Tainan 70428, Taiwan. E-mail: leonguo@mail.ncku.edu.tw

CDF (1090 parts per trillion versus 28 ppt), and 128 times background for the 1,2,3,4,7,8 hexa CDF (2560 ppt versus 20 ppt)⁶. Background exposure to these compounds is common throughout the world, and, because these poisonings represent the only community exposures to PCBs and PCDFs in which detectable morbidity and mortality have occurred, there has been considerable scientific and regulatory interest in them.

Children born to Yucheng women up to 6 years after the exposure have ectodermal defects, developmental delay, and disordered behaviour⁷ and the whole cohort has excess mortality from non-malignant liver disease after 13 years of follow-up.⁸ Following the study on mortality, which produced current addresses for the Yucheng victims, the Taiwan National Science Council funded a morbidity survey confined to surviving members of the cohort and controls who were ≥ 30 years in 1993. Because there is both laboratory evidence^{9,10} and evidence from the Japanese poisoning¹¹ that female reproductive function might be affected, the women's interviews included questions about menstrual function and reproductive performance.

Materials and Methods

This study was reviewed and approved by the Institutional Review Board at National Cheng Kung University Medical College. The Yucheng registry and the mortality follow-up are described elsewhere.⁸ From 1979 to 1983, the Taiwan Provincial Department of Health registered 2061 cases based on signs and symptoms of the illness or a history of consumption of the contaminated oil. Participation in the registry was voluntary, but since it provided access to free examinations and medical care, and there was much local publicity at the time, registration is thought to be complete. We acquired the registry from the Department of Health in 1991.

Taiwan has local household registration offices in every village, town, and city precinct. The registration offices, among other functions, keep records of deaths, record changes of residence, and maintain forwarding addresses. Using the address listed in the Yucheng registry, we began in 1992 to locate each subject's record at their registration office, and traced them to 31 December 1991. Among the 2061 subjects included in the Yucheng registry, 70 were actually offspring of the exposed subjects who were born during or after the incident, and so were excluded. Of the remaining 1991 Yucheng subjects, 154 (8%) had the wrong or no address and could not be traced further, leaving 1837 subjects who were located through their neighbourhood household registration offices' records. Of the cohort, 986 (54%) of those located were female, of whom 36 had died by 31 December 1991.⁸ The overall morbidity survey¹² of which the women's reproductive study was a part was limited to those ≥ 30 years of age in 1993, in whom the majority of health impairment was expected to occur. In addition, the women's reproductive study was limited to women who were ≤ 59 in 1993, and thus ≤ 45 when the exposure occurred in 1979 and therefore likely to have been pre-menopausal then. There were 600 such women alive on 31 December 1991. We attempted to find and interview all of them.

Ideally, a control group would have been identified at the time of the poisoning from the areas where the poisoning occurred and then followed in the same way as the exposed group. No such control group was established at the time. There

were no telephone books, city registries, or other archival material that listed the residents in the towns where Yucheng had occurred in 1979 and from which we could draw a contemporaneous control sample. Therefore, we used the 1979 addresses of the registry members as index addresses and attempted to identify the people who lived nearby in 1979 from the archives of the registration offices. We did this systematically beginning with the higher or lower numbered dwelling at random; we located the record of the current household, and, if that family had not been there in 1979, we worked through the archived records until we found the record of the family who had lived there. We then enumerated the family members and attempted to identify a control subject within the family. Control subjects were required to be of the same sex, within 3 years of age of the index registry member, and could not themselves be in the registry; if a household contained no eligible control subject, the next closest household was tried. We identified three controls for each registry member, and we attempted to contact the control subject living nearest to the index address in 1979. We only used one of any triplet set. We found 594 control women in the eligible age range.

The interviews took place between July 1993 and June 1994. About 95% of the women were interviewed by telephone by either a trained college student or research assistant, in Taiwanese or Mandarin as the woman preferred. The others, mostly women with no home phone, were interviewed in their homes. The interviewers described the study as a health survey conducted by Cheng Kung University Medical College, and did not mention Yucheng or PCBs specifically. The interviewers were not told the exposure status of the subject; however, some women volunteered that they had been Yucheng victims. The interviewers were not, however, specifically aware of hypotheses concerning reproductive or menstrual dysfunction. The questions about menstrual cycles referred to usual or typical cycles. We did not attempt to have only female interviewers interview female subjects.

Although the selection of controls was a matched procedure, some of the exposed subjects had no match among the successfully interviewed controls, and some of the exposed subjects for which there were interviewed controls were not successfully interviewed. Thus, when we compared frequencies or means, we used unpaired χ^2 and T tests. Analyses were carried out using the Statistical Analysis System for the personal computer (PC SAS) from the SAS Institute, Cary, NC. Although we had hypotheses derived from the experience of the Japanese Yusho women, animal studies, and our previous studies of the children of these women, this study was also descriptive, and we made no adjustment for multiple statistical comparisons. Not all women answered all questions, and the frequencies are based on the number of responses other than 'don't know' or equivalent.

Between 1979 and 1981, the Health Department measured serum PCB levels of many members of the Yucheng cohort.³ These results were used to stratify participating Yucheng women into high and low exposed groups. Of the 600 exposed women, four had died between the end of the mortality follow-up in 1991 and interview in 1993–1994. We were able to contact 368 of the remaining women. The others either had wrong or incomplete addresses, no telephone listing, or could not be contacted at the listed number after three attempts. Of the 594 controls, three had died between 1991 and 1993, and

we were able to contact 329 of them. Twelve of the exposed women and 17 of the controls refused to be interviewed, and so we had usable interviews from 356 exposed and 312 controls.

Results

The 356 Yucheng women who participated are older than the 244 Yucheng women who did not participate, but their serum PCB values are similar (Table 1). The participating Yucheng and control women were very similar in age distribution (Table 2). About 50% of each group were 30–39 years of age. Over 90% of both groups were married. About two-thirds of both groups received no or only primary education. Less than 2% of the women used tobacco or alcohol regularly.

More than twice as many Yucheng women reported typically having abnormally light menstrual periods, (8.8% versus 3.4%); there was little difference in the frequency of reported heavy periods (6.0% versus 4.1%), and only Yucheng women reported that they had both abnormally heavy and light periods (6 women, 1.8% versus 0). Overall, the percentage reporting abnormalities of menstrual flow was 16.6% versus 7.5% ($P < 0.05$). The percentage reporting irregular cycles, dysmenorrhoea, the reported frequency of sexual intercourse, the percentage who had experienced menopause and the mean age at menopause were similar in the Yucheng women and the controls (Table 3).

Between 1979 and 1981, 258 of the Yucheng women in this study had serum PCB levels measured by the Health Department.³ If we divide the exposed women into those with PCB levels ≤ 46 ppb, the median, and those with higher levels, then there is little evidence for dose-response (Table 3). Yucheng women who had PCB analyses done were 2 years older, 41.7 ± 0.5 versus 39.7 ± 0.5 (mean \pm SE), probably because of reluctance to draw blood from the younger victims when they were teenagers in 1979–1981. Thus, the fraction reporting menopause among the women with PCB levels is higher than in all the Yucheng women.

Among the Yucheng women, 342 (of the 356) had ever married, and among the controls 302 (of 312) had ever married. Only four of these Yucheng women and three controls had no living children. The average number of living children was the same in both groups, 3.1 (Table 4). The Yucheng women reported stillbirths since 1979 2.5 times more frequently than the controls ($P = 0.068$), but spontaneous abortion frequency was similar in both groups. Among the Yucheng women, 33 (10%) reported 35 deaths among their offspring during childhood, and 18 (6%) control women reported 18 deaths. Among the deaths reported by the Yucheng women, eight had no dates reported, nine (33%) occurred before 1979 (unexposed children), three (11%) occurred during or after 1979 to children born before 1979 (directly exposed children), and 15 (55%) occurred in children born during or after 1979 (transplacentally exposed children). Among the deaths reported by the control women, four had no dates recorded, five (36%) occurred before 1979, three (21%) occurred during or after 1979 in children born before 1979, and six (43%) occurred in children born during or after 1979. The numbers of women who reported needing longer than a year to get pregnant or getting treated for infertility were small and we did not divide them into time periods, but there appears to be no differences. There is no

Table 1 Age and serum polychlorinated biphenyl (PCB) levels of Yucheng women, by participation status, 1993–1994

Variable	Participants (N = 356) %	Non-participants (N = 244) %
Age (years)		
30–39	51.1	77.0*
40–49	32.0	17.0
50–59	16.9	6.0
Serum PCB level in 1979–1981 (N = 258) (N = 149)		
<1 $\mu\text{g/g}$ serum	2.3	0.7
1–49 $\mu\text{g/g}$ serum	52.7	58.4
50–99 $\mu\text{g/g}$ serum	24.4	29.5
100–499 $\mu\text{g/g}$ serum	19.4	10.7
≥ 500 $\mu\text{g/g}$ serum	1.2	0.7

* $P < 0.05$

Table 2 Demographic characteristics of the Yucheng and control women, 1993–1994

Characteristic	Yucheng women (N = 356) %	Control women (N = 312) %
Age group (years)		
30–39	51.1	51.6
40–49	32.0	30.1
50–59	16.9	18.3
Marital status		
Single	3.9	3.2
Married	91.6	93.6
Divorced or widowed	4.5	3.2
Education years (N ^a = 311)		
0–6	63.6	66.1
7–12	30.7	29.7
13–16	5.7	4.2
Smokers (N ^a = 311)		
	0.8	0.6
Alcohol consumption (N ^a = 355) (N ^a = 311)		
None	89.9	90.0
<1 drink/week	9.0	8.0
≥ 1 drink/week	1.1	1.9

^a Number responding to the question with an answer other than 'don't know'.

strong evidence that those with higher PCB levels had greater effects.

A higher percentage of Yucheng women had decided to limit childbearing because of health problems (7% versus 2%, $P < 0.05$), most frequently citing their PCB poisoning (Table 4). Yucheng women who limited childbearing either because of PCB exposure or for another health reason have fewer children than Yucheng women who did not report limiting childbearing. These latter women are similar to controls (Table 5), but all of these comparisons are based on small numbers of women.

Table 3 Menstruation and frequency of intercourse among Yucheng and control women, by serum polychlorinated biphenyl (PCB) level from 1979–1981 and by exposed/control status, 1993–1994

Variable	All Yucheng women (N = 356)	Control women (N = 312)	Yucheng women serum PCB $\leq 46 \mu\text{g/g}$ (N = 131)	Yucheng women serum PCB $> 46 \mu\text{g/g}$ (N = 127)
Irregular menstrual cycle	58/335, 17.3%	45/292, 15.4%	22/126, 17.5%	23/115, 20.0%
Abnormal menstrual flow	55/331, 16.6%	22/293, 7.5%*	23/126, 18.3%	20/113, 17.7%
Dysmenorrhoea	34/319, 10.7%	26/280, 9.3%	12/121, 9.9%	13/107, 12.1%
Frequency of intercourse (per month)	(N = 279) 3.6 \pm 0.18	(N = 238) 3.6 \pm 0.18	(N = 115) 3.5 \pm 0.3	(N = 82) 3.5 \pm 0.3
Experienced menopause	75/347, 21.6%	68/306, 22.2%	34/130, 26.2%	33/122, 27.0%
Mean age at menopause	(N = 60) 47.3 \pm 0.76	(N = 58) 46.7 \pm 0.94	(N = 30) 46.7 \pm 1.1	(N = 24) 47.9 \pm 1.1
Cause of menopause	(N = 61)	(N = 66)	(N = 27)	(N = 30)
Natural	51	52	21	26
Surgical	9	13	5	4
Other	1	1	1	0

* $P < 0.05$, all Yucheng women vs. controls.

Entries in rows 1–3 and 5 are number reporting the item/number responding to the question with an answer other than 'don't know', and the equivalent per cent.

In rows 4, 7 and 9, n = number responding with an answer other than 'don't know'.

In rows 5 and 8, entries are mean \pm SE.

Table 4 Reproductive outcome among ever-married Yucheng and control women, by 1979–1981 serum polychlorinated biphenyl (PCB) level and by exposed/control status, 1993–1994

Variable	All Yucheng women (N = 342)	Control women (N = 302)	Yucheng women serum PCB $\leq 46 \mu\text{g/g}$ (N = 130)	Yucheng women serum PCB $> 46 \mu\text{g/g}$ (N = 120)
Mean no. of living children	3.1 \pm 0.1, N = 340	3.1 \pm 0.1, N = 298	3.1 \pm 0.1, N = 130	3.2 \pm 0.1, N = 120
Spontaneous abortion since 1979	23/336, 6.8%	22/297, 7.4%	7/127, 5.5%	7/113, 6.2%
Stillborn infant since 1979	14/336, 4.2%	5/297, 1.7%*	5/127, 3.9%	6/113, 5.3%
Ever had a child die before adolescence (see text for dates)	33/331, 10.0%	18/294, 6.1%**	15/126, 11.9%	14/118, 11.9%
Ever took longer than one year to become pregnant	9/332, 2.7%	9/296, 3.0%	3/128, 2.3%	2/117, 1.7%
Ever had a diagnosed fertility problem	5/332, 1.5%	6/295, 2.0%	2/128, 1.6%	1/117, 0.9%
Ever decided to limit childbearing for health reason	23/335, 6.9%	6/295, 2.0%**	11/130, 8.5%	8/117, 6.8%
Reason	(N = 15)	(N = 3)	(N = 8)	(N = 4)
Reproductive system	1	3	1	0
Other system	3	0	1	1
PCB poisoning	11	0	6	3

* $P = 0.068$, all Yucheng women versus controls; ** $P < 0.05$, all Yucheng women versus controls.

In row 1, entries are mean \pm SE. Entries in rows 2–7 are number reporting the item/number responding to the question with an answer other than 'don't know', and the equivalent per cent. Row 8 entries are the number of women giving any specific answer, and in rows 9–11 the number of women giving the specific answer.

Discussion

In this retrospective survey, about twice as many Yucheng women as controls reported having abnormal menstrual flow; they did not, however, report more irregular or painful cycles, different age at menopause, or differences in frequency of sexual intercourse. They were not asked about more specific conditions such as endometriosis or fibroids. More of the Yucheng women had decided to limit childbearing because of health problems. However, Yucheng women who did not choose to limit their

family size had the same number of children as controls, arguing against a severe impairment of their fertility. Although more of the Yucheng children were stillborn or died during childhood, the mean number of living children among Yucheng and control families was the same.

In 1970, 2 years after the Yusho incident, irregular menstrual cycles were reported by 58% of 81 female Yusho patients, and urinary excretion of oestrogens, pregnanediol, and pregnanetriol of these patients tended to be low.¹¹ We did not measure hormone levels, and the women in our study did not report so high

Table 5 Mean number of living children by decision to limit childbearing in Yucheng and control women, 1993–1994

	No. of women	Mean no. of living children
Yucheng women who limited childbearing because of PCB ^a exposure	11	2.4
Yucheng women who limited childbearing because of another health problem	4	2.5
Control women who limited childbearing because of a health problem	3	2.3
Yucheng women who did not limit childbearing for a health reason	312	3.1
Control women who did not limit childbearing for a health reason	289	3.1

^a Polychlorinated biphenyls.

a rate of irregular cycles. This may be because our interviews took place much longer after the exposure than did the interviews in the Japanese study.

There are a number of limitations to our study. The women were interviewed years after the exposure, and not all were studied. The 356 Yucheng women who participated in the survey represent only 59% of the 600 women who were eligible. While women who were harder to find and interview may have had different health outcomes from those easier to locate, we know of no obvious reason for this to be so. Participating women were older; however, based on serum PCB levels drawn around the time of the incident, there was little difference in exposure between the participating and non-participating women.

The women were recalling events that were years in the past at the time of the interview, and the Yucheng women may have recalled events differently from controls. The interviewers did not present the study as a Yucheng study, but rather as a general health survey. In addition, the Yucheng women reported only one characteristic of the menses, abnormal flow, more frequently than controls. Thus, there does not appear to be a general recall or reporting bias in the data.

Monkeys exposed to PCBs had increased rates of spontaneous abortion, stillbirth, and failure to conceive.⁹ Rats exposed to PCBs via their mother's milk had long-term reproductive impairment.¹³ The PCDFs have not been studied for female reproductive toxicity, but they generally have intermediate toxicity between PCBs and the chemically similar polychlorinated dibenzodioxins (PCDDs).¹⁴ The most potent PCDD, 2,3,7,8-tetrachloro-dibenzodioxin (TCDD), is one of the most carcinogenic and fetotoxic synthetic compounds known. TCDD and similar compounds can interact with the oestrogen receptor, acting as both agonists and antagonists, and can also affect hormone status by inducing the activity of the enzymes responsible for steroid hormone metabolism. Monkeys exposed to TCDD had decreased fertility, an inability to maintain pregnancy, reduced plasma concentrations of oestrogen and progesterone, and signs of ovarian dysfunction such as anovulation and

suppression of the oestrous cycle.¹⁵ Monkeys exposed to very low doses of TCDD (5 and 25 ppt for 4 years) and then examined 10 years after exposure ceased, had dose-related increases in endometriosis prevalence (3/7 and 5/7 animals, respectively) with historical control rates of about 30–33%.¹⁰ This study, while small, was a major consideration in the World Health Organization's 1998 lowering of the tolerable daily intake for TCDD,¹⁶ because it was one of the studies showing toxicity at the lowest dose. Such effects, called 'critical effects' in regulatory toxicology, can determine advisory and regulatory outcomes for a chemical. In this case, because the PCBs, PCDFs, and PCDDs are qualitatively similar, data on reproductive function of PCB/PCDF exposed women becomes very desirable. Experimental studies in animals often have small numbers, high doses, and the studied physiology may not reflect that seen in human beings. In this particular case, there is no completely adequate animal model of the human menstrual cycle.

Our findings suggest that Yucheng women exposed to high doses of PCBs/PCDFs have relatively mild interference with menstrual function, and no change in fertility as measured by family size, requirement for infertility treatment, or libido as measured by frequency of intercourse. They do report more frequent stillbirths and higher mortality among their children, and from other studies it is known that their surviving children have excess ectodermal defects, developmental delay, and disordered behaviours.⁷ They were not asked specifically about endometriosis, the outcome of most current concern for advisory purposes, but the women did not complain of dysmenorrhoea or decreased fertility, the most common endometriosis-related symptoms. It is possible that the abnormal flow they report is related to endometriosis, but that symptom is non-specific and could be due to the oestrogenic, anti-oestrogenic, or enzyme-inducing properties of the compounds. These women had exposures high enough to make them clinically ill. Their experience should represent the upper bound of expected toxicity from background exposures. Given the extensive experimental literature on the reproductive toxicity of the PCBs and similar compounds, we think it very likely that there is menstrual dysfunction in these women, and that further study to determine the extent of dysfunction and its mechanism, especially among the younger women, is warranted.

Acknowledgements

Supported by grants from the National Science Council of Taiwan, NSC 81-0421-B-006-06YZ and NSC 83-0421-B-006-064YZ. Dr Rogan was the recipient of a 3-month NSC Visiting Scientist grant at National Cheng Kung University during some of the writing of this paper.

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